

PATENT COOPERATION TREATY *IPM/ MMC/Julie*

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

JUL 1 2005

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

Date of mailing *29/06/2005*  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220 *PR 60742 WO*

FOR FURTHER ACTION  
See paragraph 2 below

International application No.  
PCT/US2005/005754

International filing date (day/month/year)  
23.02.2005

Priority date (day/month/year)  
24.02.2004

International Patent Classification (IPC) or both national classification and IPC  
A61K31/136

Applicant  
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Docket No: *PR 60742 WO*  
Attorney: *MMC*  
Paper: *Written Opinion*  
Due Date: *29 Aug 2005*  
Deadline:  
Recorded: *9*

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 eprmu d  
Fax: +49 89 2399 - 4465

Authorized Officer

Ganschow, S

Telephone No. +49 89 2399-7807



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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
 This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:  
 a sequence listing  
 table(s) related to the sequence listing
  - b. format of material:  
 in written format  
 in computer readable form
  - c. time of filing/furnishing:  
 contained in the international application as filed.  
 filed together with the international application in computer readable form.  
 furnished subsequently to this Authority for the purposes of search.
3.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,  
 claims Nos. 1-4,7-10

because:

the said international application, or the said claims Nos. 1,9 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-4,7-10 are so unclear that no meaningful opinion could be formed (*specify*):  
**see separate sheet**

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the whole application or for said claims Nos.

the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	<input type="checkbox"/> has not been furnished <input type="checkbox"/> does not comply with the standard
the computer readable form	<input type="checkbox"/> has not been furnished <input type="checkbox"/> does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

See separate sheet for further details

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or  
industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	5,6,11
	No: Claims	
Inventive step (IS)	Yes: Claims	5,6
	No: Claims	11
Industrial applicability (IA)	Yes: Claims	2-8,10,11
	No: Claims	

2. Citations and explanations

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to industrial applicability**

Claims 1 and 9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 1-4,7-10 lack a definition of the active compound to be used and/or the disease to be treated (lack of clarity, see item VIII). It is therefore not possible to establish an opinion with regard to novelty, inventive step and industrial applicability.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Documents**

- 1.1. The present application relates to the use of LRH1 (liver receptor homolog 1) activators in medicine.
- 1.2. The following document (D) is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: DAVIS J M ET AL: "CONVERGENT SYNTHESIS OF AMINOBICYCLO[3.3.0]OCTENES USING ZIRCONIUM CHEMISTRY AND UNUSUAL ANTI-1,3-AMINE SHIFT" SYNLETT, THIEME VERLAG, STUTTGART, DE, no. 2, February 1994 (1994-02), pages 110-112,

XP001206753 ISSN: 0936-5214

D2: FAYARD ELISABETH ET AL: "Liver receptor homolog 1 controls the expression of carboxyl ester lipase." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 37, 12 September 2003 (2003-09-12), pages 35725-35731, XP002332180  
ISSN: 0021-9258

**2. Novelty and inventive step**

- 2.1. D1 teaches the synthesis of 1-anilino-bicyclo[3.3.0]oct-2-enes (see structure **ba**). However, D1 does not refer to any medical use of these compounds.
- 2.2. None of the prior art documents teach or suggest the use of the 1-anilino-bicyclo[3.3.0]oct-2-ene with structure **ba** (see D1) in medicine (such as treating atherosclerosis or obesity). Novelty and inventive step (Article 33(2) and (3) PCT) can therefore be acknowledged (**claims 5 and 6**).
- 2.3. According to D2, LRH-1 plays an important role in cholesterol homeostasis. Thus, it would have been obvious and related with a reasonable expectation of success to try to identify compounds that will be useful in treating cholesterol-related diseases by determining whether the compound interacts with LRH1 (**claim 11**: lack of inventive step pursuant to Article 33(3) PCT).

**3. Method of treatment**

- 3.1. For the assessment of the present claims 1 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

**PCT/US2005/005754**

**Re Item VIII**

**Certain observations on the international application**

1. Claims 1,2,7,8,9 and 10 relate to a method of treating a **disease or condition caused by low plasma apoA-1-levels**. This term gives no clear limitation to medically recognised and clearly defined diseases to be treated. In the absence of a clear definition of the disorders intended in claim 1, the skilled man is left in a doubt as to the real scope of protection to be sought (Art. 6 PCT).
2. The active principle according to the claims are defined by a functional feature, namely a LHR1 activator or agonist.

The functional features embrace not only compounds which are structurally close to each other, but also any compounds that are already known to treat the diseases but for which that mode of action has not been identified and any compound yet to be discovered.

A skilled person cannot reduce to practice a definition of the claimed subject matter because the compounds employed in claims 1-4 and 7 have potentially limitless structural possibilities, and so there is absolutely no limit to the structural variation in the compounds which might act as LHR1 activator or agonist, including compounds which have yet to be made.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (**other than the one that is particularly disclosed in the application**) would fall within the scope of what is claimed.

Claims 1-4 and 7 are not clear since they totally lack a structural definition of the LHR1 activator or agonist to be used. This structural definition is considered as essential technical feature of the invention. In the absence of such a definition, the Examining Division holds that the skilled person cannot implement the claimed invention **over the whole scope claimed without undue burden**.